neovascularization with the formula of R'-Glu-Trp-R" or pharmaceutically acceptable salts thereof,

wherein R' and R" is absent or a moiety independently selected from the group consisting of an amide, an imide, an ester, an anhydride, an ether, a methyl-alkyl ester, an ethyl-alkyl ester, an alkyl group, and an aryl group,

wherein R' can also represent an amide bond between the amine of said Glu and the side chain carboxylate of said Glu,

wherein R' is present if R" is absent,

wherein both R' and R" are not both amide, and

wherein the formula weight of said compound is less than about 5000 Daltons.

20. (Once amended) The method of claim 18, wherein said compound is selected from the group consisting of:

Ac-Glu-Trp, Suc-Glu-Trp, Cpr-Glu-Trp, But-Glu-Trp, and pyroGlu-Trp

wherein Ac represents acetyl, Suc represents succinyl, Cpr represents cyclopropyl and But represents butyryl.

REMARKS

The amendment to the specification inserting Sequence ID Nos. contains no new matter.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-7, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

Attached hereto is a marked-up version of the changes made to the Specification and claims by the current Amendment. The attached pages are captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

All claims in this application stand rejected under 35 U.S.C. 112 on various grounds. The above amendments correct a typographical error in claim 18 that the examiner considered to be an obvious error, limit the claims to the elected invention, and add definitions of symbols included in claim 20. No new matter is considered introduced by these amendments.

The claims also stand rejected as indefinite as to the process steps and endpoint. The examiner considers that the claims are indefinite in not reciting that the compounds are administered for an effective time and under conditions so as to be effective. Applicants respectfully disagree that the claims are indefinite for this reason.

First, Applicants point out that claims with the current language were granted in the parent application, SN 09/260,190, now US patent 6,096,713 (copy attached). Applicants should be entitled to claims of the same scope here.

Second, the examiner has provided no reasons for this rejection nor for why the claims are regarded as indefinite. Such reasons are necessitated under Rule 104(a)(2).

In addition, Applicants submit that the claims properly define and distinctly claim what is regarded as the invention, namely that an amount of the claimed compounds are administered that is effective to inhibit neovascularization. The standard of whether a claim is indefinite is whether its scope is clear to one skilled in the art, reading the claim in light of the specification. North American Vaccine Inc. v. American Cyanamid Co., 28 USPQ2d 1333, 1339 (Fed. Cir. 1993; Miles Laboratories, inc. v. Shandon, Inc., 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). The claim is indefinite if it fails to delineate, to one skilled in the art, reading it in light of the specification, the boundary between what is claimed and what is not. Ex parte LeMoine, 46 USPQ 2d 1420, 1424 (BOPAI, 1994). However, the failure to include process conditions does not by itself render a claim indefinite. See e.g. Ex parte Clark, 174 USPQ 40 (Bd. App., 1971).

Applicants submit that the claims as amended fully meet the requirements of Section 112 and request withdrawal of these rejections.

All claims under examination stand rejected as obvious over Nishimura or Ryan in view of Rodgers. This rejection is considered to be untenable.

The claims under examination call for inhibition of neovascularization by a dipeptide derivative. The derivative has the formula R'-Glu-Trp-R" in which R' and R" are independently absent (but one of them must be present) and are selected from various groups including amides, esters, alkyls, etc., but not including amino acids.

Ryan describes treating hypertension with peptides having a nine-amino acid configuration, as described in column 5. The examiner characterizes this reference as disclosing "peptide inhibitors of ACE that begin with the dipeptide pGlu-Trp", and acknowledges that the reference does not teach inhibition of neovascularization or angiogenesis.

Nishimura is cited for its disclosure at column 10 of another peptide that "begins with the dipeptide pGlu-Trp, and inhibits ACE" but admittedly is not disclosed as inhibiting neovascularization of angiogenesis. This peptide, too, is a nine-amino acid peptide.

Neither reference discloses a dipeptide as claimed. Both disclose substantially larger peptides that have in common with the claimed substances only the fact that they begin with the same two amino acids. Neither reference contains any disclosure attributing the disclosed activity, or indeed any activity, of those longer peptides, to the two-acid combination Glu-Trp or to its derivatives. Neither reference discloses anything about activity of any type, of Glu-Trp dipeptides or their derivatives.

The fact that a longer peptide contains a shorter peptide, of itself, provides no information or basis for a conclusion that the shorter peptide would have similar activity to the longer one. Many examples exist of short peptides that have very different activity than longer peptides that contain them. A change in one or two amino acids of a peptide, or a shortening or lengthening of the chain, can alter activity and/or create a new

pharmacological entity. Just to mention one example, angiostatin, a smaller peptide derived from plasminogen, has anti-angiogenic activity, whereas plasminogen does not.

In short, the disclosures of Ryan and Nishimura are simply irrelevant to activity or expected activity of the claim-designated peptides.

Rodgers, as pointed out by the examiner, does not relate to peptides having a Glu-Trp sequence. It is cited for the proposition that angiotensin stimulates neovascularization and angiogenesis, and the conclusion is drawn that therefore an ACE inhibitor such as those disclosed in Ryan and Nishimura would be expected to inhibit neovascularization and angiogenesis.

First, as mentioned above, neither Ryan nor Nishimura is pertinent to the claimed peptides. Therefore, the addition of Rodgers, which does not even disclose a longer chain peptide containing the Glu-Trp sequence, does not make up for this deficiency.

Secondly, Rodgers does not specifically state that angiotensin stimulates neovascularization, but attributes that to prior art publications describing specific research, i.e., is a type of hearsay and in any event not a general statement.

Thirdly, the reasoning proposed by the examiner lacks a sound scientific basis. The combination of references is said to support the following proposition: (a) inhibitors of ACE inhibit angiotensin II; (b) angiotensin II is a potent vasoconstrictor and has been found in some research to stimulate angiogenesis; (c) therefore, an ACE inhibitor would be expected to inhibit neovascularization.

This oversimplifies the situation. Inhibition of angiotensin II, by whatever substance, may or may not be a determining factor in whether that substance also inhibits neovascularization or angiogenesis. Other factors will be involved in such activity, and may in fact prove to be the major factors in establishing the activity. There is no basis in the references for setting up such a direct relationship between ACE/angiotensin II inhibition and inhibition of neovascularization.

For the above reasons, Applicants submit that the rejection of claims as obvious over the cited references lacks basis and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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#1306251 v1 - First amendment

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at page 3, line 9, has been amended as follows:

--As used herein, a derivative of the R'-Glu-Trp-R" dipeptide includes those in which the dipeptide is derivatized by the covalent attachment of a moiety at R' and/or R". This includes, for example, pharmaceutically acceptable salts of the dipeptide, amides, imides, esters, anhydrides, ethers, methyl or ethyl-alkyl esters, alkyl, aryl or mixed alkyl/aryl derivatives wherein the formula weight is less than about 5000 Daltons or less than 1000 Daltons, multimeric or cyclic versions of the dipeptide and peptides of fewer than about 20 amino acids or less than about 10 amino acids that include glu-trp within their amino acid sequence. Representative examples include HEW, EWEW (SEQ ID NO 1), GEW, EWKHG (SEQ ID NO 2), EWKKHG (SEQ ID NO 3), EW-NH-NH-GHK-NH2, Ac-L-Glu-L-Trp-OH, Suc-EW, Cpr-EW, But-EW, RKEWY (SEQ ID NO 4), RKEW (SEQ ID NO 5), KEWY (SEQ ID NO 6), KEW, Pew.—

The paragraph beginning at page 18, line 2, has been amended as follows:

--In this experiment saline served as a negative control and 10 μg/disk of heparin served as a positive control. The pentapeptide Tyr-Ala-Glu-Glu-Lys (TAEEK) (SEQ ID NO 7) served as a specificity control, (i.e., for possible nonspecific effects of peptides on neovascularization at the concentrations tested). Nine-12 test disks and a corresponding number of different embryos were employed for each test concentration along with 82 (each) positive and negative control embryos. The results are summarized in the following TABLE. –

In the claims:

Claims 18 and 20 have been amended as follows:

18. (Twice Amended) A method of inhibiting neovascularization in a subject in need thereof comprising:

administering to said subject a pharmaceutical preparation comprising a pharmaceutically acceptable carrier and an amount of a compound effective to inhibit neovascularization with the formula of R'-Glu-Trp-R" or pharmaceutically acceptable salts thereof,

wherein R' and R" is absent or a moiety independently selected from the group consisting of an amide, an imide, an ester, an anhydride, an ether, a methyl-alkyl ester, an ethyl-alkyl ester, an alkyl group, and an aryl group,

wherein R' can also represent an amide bond between the amine of said Glu and the side chain carboxylate of said Glu,

wherein R' is present if R" is [present if R' is] absent,

wherein both R' and R" are not both amide, and

wherein the formula weight of said compound is less than about 5000 Daltons.

20. (Once amended) The method of claim 18, wherein said compound is selected from the group consisting of:

Ac-Glu-Trp, Suc-Glu-Trp, Cpr-Glu-Trp, But-Glu-Trp, and pyroGlu-Trp

wherein Ac represents acetyl, Suc represents succinyl, Cpr represents cyclopropyl and But represents butyryl.

CLEAN PARAGRAPHS AND CLAIMS

Please replace the paragraph beginning at page 3, line 9, with the following:

--As used herein, a derivative of the R'-Glu-Trp-R" dipeptide includes those in which the dipeptide is derivatized by the covalent attachment of a moiety at R' and/or R". This includes, for example, pharmaceutically acceptable salts of the dipeptide, amides, imides, esters, anhydrides, ethers, methyl or ethyl-alkyl esters, alkyl, aryl or mixed alkyl/aryl derivatives wherein the formula weight is less than about 5000 Daltons or less than 1000 Daltons, multimeric or cyclic versions of the dipeptide and peptides of fewer than about 20 amino acids or less than about 10 amino acids that include glu-trp within their amino acid sequence. Representative examples include HEW, EWEW (SEQ ID NO 1), GEW, EWKHG (SEQ ID NO 2), EWKKHG (SEQ ID NO 3), EW-NH-NH-GHK-NH2, Ac-L-Glu-L-Trp-OH, Suc-EW, Cpr-EW, But-EW, RKEWY (SEQ ID NO 4), RKEW (SEQ ID NO 5), KEWY (SEQ ID NO 6), KEW, pEW.--

Please replace the paragraph beginning at page 18, line 2, with the following:

--In this experiment saline served as a negative control and 10 μg/disk of heparin served as a positive control. The pentapeptide Tyr-Ala-Glu-Glu-Lys (TAEEK) (SEQ ID NO 7) served as a specificity control, (i.e., for possible nonspecific effects of peptides on neovascularization at the concentrations tested). Nine-12 test disks and a corresponding number of different embryos were employed for each test concentration along with 82 (each) positive and negative control embryos. The results are summarized in the following TABLE. –

Claims

18. (Twice Amended) A method of inhibiting neovascularization in a subject in need thereof comprising:

administering to said subject a pharmaceutical preparation comprising a pharmaceutically acceptable carrier and an amount of a compound effective to inhibit neovascularization with the formula of R'-Glu-Trp-R" or pharmaceutically acceptable salts thereof,

wherein R' and R" is absent or a moiety independently selected from the group consisting of an amide, an imide, an ester, an anhydride, an ether, a methyl-alkyl ester, an ethyl-alkyl ester, an alkyl group, and an aryl group,

wherein R' can also represent an amide bond between the amine of said Glu and the side chain carboxylate of said Glu,

wherein R' is present if R" is absent,

wherein both R' and R" are not both amide, and

wherein the formula weight of said compound is less than about 5000 Daltons.

20. (Once amended) The method of claim 18, wherein said compound is selected from the group consisting of:

Ac-Glu-Trp, Suc-Glu-Trp, Cpr-Glu-Trp, But-Glu-Trp, and pyroGlu-Trp

wherein Ac represents acetyl, Suc represents succinyl, Cpr represents cyclopropyl and But represents butyryl.